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EXAMINER	
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ART UNIT	PAPER NUMBER
1637	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/617,979	HENKIN ET AL.	
	Examiner	Art Unit	
	Samuel Woolwine	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *1-17 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Claims 1-35 are pending in the application. Claims 1-17 and 35 are currently withdrawn from consideration, being drawn to a non-elected invention. Claims 29 and 30-34 were indicated allowable in the previous Office action (OA 11/01/2006). However, upon further consideration, new grounds of rejection have been applied as outlined below. This Office action is NON-FINAL.

Response to Arguments

The rejections made in OA 11/01/2006 are withdrawn in view of Applicant's declaration filed 05/01/2007, which effectively removes the Grundy et al (2002) reference as prior art.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. These claims recite the limitation "glycine synthase leader", whereas the remainder of the specification (and claims 30-34) refers to *glyQS*, which encodes glycyl tRNA synthetase (see abstract, for example). Therefore, it is unclear as to what Applicant is referring by the term "glycine synthase". If this is an error, Applicant may overcome the rejection by amending to "glycyl tRNA synthetase".

If Applicant intends some other gene, Applicant is invited to provide a glycine synthase gene from a Gram positive bacterium known in the prior art and indicate that such a gene has a "T-box". In this case, Applicant is requested to confirm that these claims are not drawn to glycyl tRNA synthetase, but to glycine synthase as claimed. For purposes of examination over the prior art, the examiner will assume "glycine synthetase" means "glycyl tRNA synthetase".

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 18-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over van de Guchte et al (Microbiology, 2001, vol 147, pp 1223-1233, cited on the IDS of 10/17/2003) in view of Landick et al (Methods in Enzymology, 1996, vol 274, pp 334-

353), Kirschbaum et al (USPN 6,174,722 B1), Edwards et al (USPN 5,578,444) and Schimmel et al (The FASEB Journal, 1998, vol 12, pp 1599-1609).

With regard to claim 18, van de Guchte taught *a template DNA that comprises: (i) a bacterial promoter* (trp promoter; see figure 2), *(ii) a leader of a T-box regulated gene, including a transcription start site* (trp leader; see figure 2), *and (iii) a downstream polynucleotide of sufficient length for detection of a read-through mRNA product* (trpE-lacZ fusion; see figure 2; see also the detected read-through mRNA products in figure 3). As van de Guchte was performing an *in vivo* transcription assay, he also implicitly taught *divalent metal cations* (i.e. Mg^{2+}), *nucleoside triphosphates*, *bacterial RNA polymerase complex* and *tRNA specific for a specifier sequence located in the leader*, all of which would have inherently been present in the cells of *L. lactis* he used (see figure 3 caption). Furthermore, van de Guchte explained the mechanism whereby trpE, like other amino acid biosynthetic and aminoacyl tRNA synthetase genes in Gram-positive bacteria, is regulated at the level of transcription through interaction of the nascent RNA transcript with a specific tRNA (see Introduction).

With regard to claim 19, Mg^{2+} would have inherently been present in the cells of *L. lactis* used by van de Guchte (see figure 3 caption).

With regard to claim 20, all of these nucleoside triphosphates would have been inherently present in the cells of *L. lactis* used by van de Guchte, since these are the building blocks used by all living cells to synthesize RNA.

With regard to claim 22, van de Guchte also taught that *B. subtilis glyQS* and its corresponding regulatory $tRNA^{Gly}$ fell into this family of T-box regulated genes (see last item in figure 6).

With regard to claim 23, based on the comprising language of the claim, van de Guchte taught a downstream polynucleotide of sufficient length for detection of a read-through mRNA product which *comprises* a polynucleotide which is from about 30-150 nucleotide residues in length (van de Guchte's constructs are in the chromosome of *L. lactis*, which *comprises* a polynucleotide which is from about 30-150 nucleotides). In any event, van de Guchte clearly taught a downstream polynucleotide of sufficient length such that visualization of read-through mRNA products was possible (see figure 3), and limitations directed to mere differences in the size of the visible transcript do not patentably distinguish over van de Guchte's teachings absent secondary considerations.

With regard to claim 24, van de Guchte taught *B. subtilis* $tRNA^{Gly}$ (see last item, figure 6).

With regard to claim 26, van de Guchte taught a system wherein the leader comprised a polynucleotide which was a variant of a wild-type leader from a Gram positive bacterial strain, wherein the variant comprised modifications to the wild-type specifier sequence (see page 1225, first paragraph of Results).

With regard to claim 27, van de Guchte taught a system wherein the tRNA specific for a specifier sequence located in the leader is a variant of a wild-type tRNA wherein the wild-type anticodon is altered to complement with the leader sequence (see

page 1227, first paragraph under "Effect of chimeric tRNAs on transcription antitermination in the specifier Asn mutant"; specifically: "a gene was created based on the $tRNA^{Trp}$ gene in which the anticodon CCA (anti-TGG, Trp) was replaced by GTT (anti-AAC, Asn)").

With regard to claim 28, this claim simply combines the limitations of claims 26 and 27, which have been addressed immediately above.

With regard to claim 30, van de Guchte taught *a bacterial transcription assay system which comprises a template DNA comprising: (i) a bacterial promoter* (trp promoter; see figure 2), *(ii) a polynucleotide comprising a leader, including a transcription start site* (trp leader; see figure 2), *and (iii) a downstream polynucleotide of sufficient length for detection of a read-through mRNA product* (trpE-lacZ fusion; see figure 2; see also the detected read-through mRNA products in figure 3)*; RNA polymerase* (this would have inherently been present in the *L. lactis* cells used by van de Guchte; see figure 3 caption), *and uncharged tRNA* (this would also have been inherently present in the *L. lactis* cells used by van de Guchte, particularly in the cells grown on medium lacking Asn or Trp; see figure 3 caption and see page 1224, column 2, "RNA manipulations"). van de Guchte also taught that *B. subtilis glyQS* and its corresponding regulatory $tRNA^{Gly}$ fell into this family of T-box regulated genes (see last item in figure 6).

With regard to claim 31, van de Guchte also taught that *B. subtilis glyQS* and its corresponding regulatory $tRNA^{Gly}$ fell into this family of T-box regulated genes (see last item in figure 6).

With regard to claim 33, van de Guchte taught a system wherein the leader comprised a polynucleotide which was a variant of a wild-type leader from a Gram positive bacterial strain, wherein the variant comprised modifications to the wild-type specifier sequence (see page 1225, first paragraph of Results).

With regard to claim 34, van de Guchte taught a system wherein the tRNA specific for a specifier sequence located in the leader is a variant of a wild-type tRNA wherein the wild-type anticodon is altered to complement with the leader sequence (see page 1227, first paragraph under "Effect of chimeric tRNAs on transcription antitermination in the specifier Asn mutant"; specifically: "a gene was created based on the $tRNA^{Trp}$ gene in which the anticodon CCA (anti-TGG, Trp) was replaced by GTT (anti-AAC, Asn)").

van de Guchte did not teach at least two assay mixtures, wherein the assay mixtures comprised dinucleotides corresponding to and encoded by the transcription start site of the leader, and wherein one of the assay mixtures further comprised a potential inhibitor substance, as required by claim 18.

van de Guchte also did not teach the particular dinucleotides recited in claim 21.

van de Guchte did not teach RNA polymerase from either *B. subtilis* or *Escherichia coli* as recited in claims 25 and 32.

van de Guchte did not teach the limitations of claims 26, 28 and 30-34 with respect to the leader being from a glycine synthetase and using variants of this leader and the corresponding regulatory tRNA (he taught the leader and regulatory tRNA for glycine synthetase (*B. subtilis glyQS* and its corresponding regulatory $tRNA^{Gly}$; see last

item in figure 6), but he did not use or create variants of this T-box-regulated gene/tRNA in his assay).

van de Guchte did not teach halted-complexes as recited in claims 29-34.

The differences between the claimed assay mixtures and those taught by van de Guchte are: (1) van de Guchte taught an *in vivo* assay, whereas the claimed assay mixtures are clearly directed to an *in vitro* system, as can be seen from the inclusion of dinucleotides (claims 18-28) and halted-complexes (claims 29-34) in the assay mixtures; (2) van de Guchte did not teach a combination of an assay mixture comprising a potential inhibitor substance and an assay mixture lacking said potential inhibitor substance; (3) van de Gucthe, while disclosing *B. subtilis glyQS* and $tRNA^{Gly}$, did not teach using those members of the T-box family in an assay mixture.

To address item (2), the concept of using *in vitro* transcription processes for screening natural products and other chemical substances was known in the art, as shown by Kirschbaum (USPN 6,174,722 B1, entitled "*In vitro* Transcription Processes For Screening Natural Products And Other Chemical Substances"). Kirschbaum specifically teaches carrying out transcription processes in the presence and absence of a substance to be tested, and determining the activity (e.g. inhibitory or activating) from the difference in the amount of transcripts produced (column 14, lines 15-28).

Furthermore, Edwards et al taught: "Antibiotics that bind to the RNA polymerase and prevent mRNA production are potent bacterial poisons: molecules that could interfere with the initiation of transcription for specific essential genes are expected to have similar effects" (column 65, lines 48-52).

Therefore, it would clearly have been *prima facie* obvious to one of ordinary skill in the art at the time the invention of the instant application was made to modify the teachings of van de Guchte to make assay mixtures with and without a potential inhibitor substance (as taught by Kirschbaum) for the benefit of screening for molecules that could interfere with transcription, and thus identify potentially useful antibiotics (as taught by Edwards).

To address item (3) above, Schimmel et al taught: "...aminoacyl tRNA synthetases are being pursued as targets for new drugs. These enzymes are universal and are essential for cell viability. The key to their usefulness lies in being able to find drugs that inhibit a pathogen synthetase but not its human cell counterpart" (abstract).

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art to apply the teachings of van de Guchte, in view of the teachings of Kirschbaum and Edwards, to the *B. subtilis glyQS* system, since *glyQS* encodes a tRNA synthetase, and since Schimmel taught these enzymes were being pursued as targets for new drugs and that their usefulness lay in being able to find drugs that inhibit a pathogen sythetase by not its human cell counterpart (note that van de Guchte taught the T-box system was unique to Gram positive bacteria; thus it would have been obvious to one of skill in the art that the uniqueness of the T-box system offered a way to inhibit a (Gram positive) pathogen synthetase but not a human one, as suggested by Schimmel).

Finally, to address item (3) above, Landick taught advantages of using dinucleotides and halted-complexes (as discussed below). Since these advantages would only have been attainable by modifying the teachings of van de Guchte to make

in vitro rather than *in vivo* assay mixtures, it would have been *prima facie* obvious to one of ordinary skill in the art to do so.

With regard to claim 18, Landick taught *in vitro* transcription assay mixtures comprising dinucleotides corresponding to and encoded by the transcription start site of the template (see page 337, figure 1 and last full paragraph). Landick also provides evidence to support the examiner's assertion that van de Guchte's *in vivo* assay must have comprised Mg^{2+}, NTPs and RNA polymerase, since Landick indicates these are necessary for transcription (page 336, line 1; page 337, last two lines).

With regard to claim 21, Landick taught the dinucleotide ApU (page 337, last full paragraph on page). In teaching how to use this dinucleotide, corresponding to the transcriptional start site for the particular template Landick was using in his assay, Landick also renders obvious all the dinucleotides recited in claim 21, since it would have been obvious to one of ordinary skill in the art to choose the dinucleotide corresponding to the transcriptional start site for any template under investigation. The 16 dinucleotides recited in claim 21 represent the whole genus of dinucleotides that are naturally found in RNA (the product of transcription by RNA polymerase). One of ordinary skill in the art would have easily envisaged this genus based on Landick's disclosed use of the dinucleotide ApU.

With regard to claims 29-34, Landick also taught halted-complexes (last paragraph on page 335, carrying over to page 336).

It would have been *prima facie* obvious to modify the teachings of van de Guchte to convert from an *in vivo* assay to an *in vitro* assay to obtain the benefit conferred by

using dinucleotides corresponding to and encoded by the transcriptional start site of the template in an *in vitro* transcription reaction. Specifically, Landick teaches:

"Some pause sites occur at strategic positions in transcriptional units where they halt elongation and facilitate the interaction of RNA polymerase or the nascent RNA with regulatory factors" (page 335, first sentence of first full paragraph);

"The primary requirement in studying transcriptional pausing is a method to synchronize transcription through the region of interest. Possibilities include forming open initiation complexes in the absence of a component necessary for productive initiation...or halting an elongating RNA polymerase at an early position in the transcriptional unit by withholding one NTP" (page 335, last paragraph carrying over to page 336);

"Halted elongation complexes offer two advantages: (i) greater synchrony during the elongation phase...and (ii) the ability to end-label the RNA transcript" (page 336, middle of first (partial) paragraph).

With regard to claims 25 and 32, Landick also taught *Escherichia coli* RNA polymerase. It would have been *prima facie* obvious to use *Escherichia coli* RNA polymerase in the *in vitro* transcription reaction because Landick taught it could be obtained commercially or purified easily (page 337, last sentence continuing on page 338). It would also have been obvious to use the RNA polymerase from *B. subtilis* when analyzing genes from *B. subtilis*, such as *glyQS*, in an *in vitro* transcription assay, since the gene, the leader sequence, the corresponding tRNA and the polymerase were designed by nature to work together.

Conclusion

No claims are free of the art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Woolwine whose telephone number is (571) 272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

scw

JEFFREY FREDMAN
PRIMARY EXAMINER
7/17/07